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BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
CAMPELL, BRUCE R	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/922,483
Filing Date: August 02, 2001
Appellant(s): FINKBEINER, STEVEN

Paula A. Borden
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 15, 2005 appealing from the Office action mailed August 12, 2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Heiser et al. Proceeding of the National Academy of Science (2000) Vol. 97, No. 12, pages 67-39-6744. (see IDS January 4, 2002).

Kaji et al. Journal of Biochemistry (2001) Vol. 129, pages 577-583.

South et al. Thrombosis and Haemostasis (1195) Vol. 73, pages 144-150.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 10-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The preamble of the claim is directed to identifying compounds capable of modulating the interaction between mutant huntingtin protein and its (cellular) targets. Yet the method steps outlined in the claim will only measure the interaction between mutant huntingtin protein and an antibody. Antibodies are not the normal cellular targets of the huntingtin protein.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Cir.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. Such an analysis does not need to specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection.

The specification shows (pages 17-18) monoclonal antibodies developed according to the protocol set out in Example I and designated 1F11E5, 4H7H7, 3A2D3, 4F1B5, 3C4A6, 3B5H10. These monoclonal antibodies were all compared to the 1C2 antibody of the prior art by Western

blot analysis. The amount of the 1C2 antibody necessary to generate a comparable Western blot signal was always greater than the amount of 1F11E5, 4H7H7, 3A2D3, 4F1B5, 3C4A6 and 3B5H10 antibodies needed. The results indicate that the disclosed antibodies are specific for mutant huntingtin over wild-type huntingtin, even when the huntingtin protein is native conformation.

The specification does not teach a method of screening agents that will interfere with the interaction of mutant huntingtin protein with the normal cellular target of the huntingtin protein. The normal cellular target of the huntingtin protein is not known. The information obtained using the claimed method steps would merely show that the agent may interfere with the antibody binding to the polyglutamine expansion protein. The methods cannot distinguish whether the agent binds to the antibody or the polyglutamine containing protein itself. If the agent only binds to the antibody it would not be useful to prevent the binding of the huntingtin protein to the undisclosed and unidentified cellular receptor.

"Although the causal relationship between aggregate and formation and disease has not been proven, genetic, neuropahtological, and biochemical evidence indicate that formation of insoluble protein aggregates plays an important role in the cellular distortions underlying HD and related glutamine-repeat disordered" (see Heiser et al. IDS submitted January 4, 2002, page 6739, column 1, 2nd paragraph). The prior art teaches that the mAB 1C2 specifically recognizes polyglutamine expansions in soluble huntingtin protein. However, the antibody does not recognize insoluble high molecular weight polyglutamine expansions. Indicating that 1C2 recognizes an elongated polyglutamine tract but not when in a fibrillar conformation (see Heiser et al. IDS Paper No. 6, page 6740). The reference teaches a screening assay that interferes with

the self-aggregation of huntingtin protein, which is thought to be the cause of the neurodegenerative disease. The reference indicates that 1C2 (monoclonal) antibody, HD1 (polyclonal) antibody as well as Congo Red are able to prevent the huntingtin protein from aggregating (see Heiser et al. IDS submitted January 4, 2002, page 6741). Neither the Heiser et al. reference nor any other reference in the prior art provide any information regarding the normal cellular target for the huntingtin protein. You cannot measure the interaction between a protein (huntingtin) and its cellular target if you do not know what the structure of the cellular target is.

There is no correlation in the prior art or the instant specification, which would indicate that a compound that interferes with the antibody binding to the polyglutamine expansion of huntingtin would interfere with the binding of the polyglutamine expansion protein to the normal cellular target. In order for an antibody to be considered a "surrogate receptor" it would have to bind the huntingtin protein at the same location that the undisclosed and unidentified cellular target binds the polyglutamine expansion of the huntingtin protein. The antibody would have to occupy the same location (space) on the huntingtin protein as the cellular target, for the antibody to be a "surrogate" cellular target. Thus, the antibody would have to interfere with the huntingtin protein binding to the cellular target. A compound that interferes with the antibody binding to the polyglutamine expansion protein can act on the antibody alone or the compound can bind to the polyglutamine expansion protein. Only those compounds that bind to the polyglutamine expansion protein may affect the binding of the protein to the cellular target. However, the instantly claimed method cannot determine to which protein (huntingtin or the antibody) the

agents bind. Therefore, the claimed method cannot determine if the agent is capable of modulating the interaction between the polyglutamine expansion protein and the cellular target.

Neither the specification nor the art has established that antibody binding to the polyglutamine expansion region of the huntingtin protein occurs in the same region that binds the unknown and undisclosed cellular target.

Appellants have cited the South et al. paper as providing evidence for the use of antibodies as a "surrogate receptor." In South et al. the antibody that recognizes the GPIb domain of the vWF can be used to screen for peptide inhibitors that inhibit the binding between vEF-GPIb binding. The critical difference between the cited paper and the instant specification is that in the South et al. reference the authors actually knew that the antibody binds to the vWF protein at a region that is required for the binding of the vWF protein to the GPIb receptor (see page 144, column 2, lines 33 to page 145, column 1, line 16). In the instant specification the antibody binds to the polyglutamine expansion protein, yet there is no correlation provided that this region is the same region that is responsible for the binding the polyglutamine expansion protein to the normal cellular target. In order for the antibody to be used as a "surrogate receptor" it is necessary to establish that the antibody and the cellular target bind to the same location on the huntingtin protein.

Appellants have cited the Kaji et al. paper as providing evidence for the use of antibodies as a "surrogate receptor" in the prior art. In Kaji et al. the antibody that inhibits the chemotactic activity of monocyte chemoattractant protein (MCP-1) can be used to screen for peptide motifs that are inhibitors of the chemotactic activity. The critical difference between the cited Kaji et al. paper and the instant specification is that in the cited paper the authors have associated an

activity that is inhibited with the antibody. In the instant specification, the examples provided teach a method of how to generate an antibody to the polyglutamine expansion protein and comparing the binding of the antibodies to an antibody, 1C2, from the prior art. The specification has not provided any evidence to show that the disclosed antibodies prevent the binding of the huntingtin protein to its unknown and undisclosed cellular target. Therefore, Appellants argument that the disclosed antibody can serve as a "surrogate receptor" is not convincing.

The preamble of the claim is directed to identifying compounds capable of modulating the interaction between mutant huntingtin protein and its cellular targets. Yet the method steps outlined in the claim will only measure the interaction between mutant huntingtin protein and an antibody. Antibodies are not the normal cellular targets of the huntingtin protein. The normal cellular target of the huntingtin protein has not been defined in the instant specification nor has it been disclosed in the prior art.

The specification does not teach a method of screening agents that "is capable" of modulating the interaction of mutant huntingtin protein with the normal cellular target of the huntingtin protein. The method steps merely indicate that the agent may interfere with the antibody binding to the polyglutamine expansion protein. The claimed method steps cannot distinguish whether the agent binds to the antibody or the polyglutamine containing protein.

There is no correlation in the prior art or the instant specification that would indicate that a compound that interferes with the antibody binding to the polyglutamine expansion of huntingtin would interfere with the binding of the polyglutamine expansion protein to the normal cellular target of huntingtin. The prior art and the instant specification are only enabled for using

antibodies to detect whether an agent can interfere with the binding of mutant huntingtin protein to itself, i.e. the agent interferes with aggregation of the polyglutamine expansion protein to itself.

The 1.132 Declaration by Ross Stein does not overcome the rejection because the declaration does not actually indicate that the antibody binds to the polyglutamine expansion protein in the same location where the cellular target binds to the polyglutamine expansion protein. "The antibody that will be used is the in this assay has specific binding for the toxic conformation of the polyglutamine" (see Ross Stein declaration paragraph 4). The toxic conformation of the polyglutamine is considered to be the fibril form i.e. the stacking of the polyglutamine expansion proteins into a large mass through the association of the polyglutamine repeat regions. Additionally, binding between polyglutamine repeat regions does not provide information regarding the binding of huntingtin to the cellular target. "It is not unreasonable to assume that the binding site on the antibody might have structural features and binding properties for polyglutamine that are similar to the binding sites on the cellular proteins that mediate the toxic effect of the polyglutamine" (see Ross Stein declaration paragraph 4). At best the declaration merely speculates that the antibody may bind in the same location as the cellular receptor. The declaration does not provide a correlation that would indicate that a compound that interferes with the antibody binding to the polyglutamine expansion of huntingtin would interfere with the binding of the polyglutamine expansion protein to the normal cellular target.

(10) Response to Argument

The following arguments were made in the instant Appeal Brief: (1) The examiner failed to establish a reasonable basis to question the enablement. (2) No conclusions as to the enablement of the instant claims can be drawn from the Heiser et al. reference. (3) Antibodies specific for a protein can serve as a surrogate for binding of that protein to a second protein. (4) Those skilled in the art would find it reasonable to use the assay methods to identify agents that inhibit binding of a protein containing a polyglutamine expansion to its cellular target.

(1) Response to argument that "the examiner failed to establish a reasonable basis to question the enablement."

In this instance, the Office did meet the burden by explaining that neither Appellants specification nor the art in general has a shown that the disclosed antibodies would inhibit the binding of the huntingtin protein (a polyglutamine expansion protein) to the cellular target. In the South et al. and Kaji et al. references cited by Appellant the antibodies that were used as "surrogate receptors" were shown to inhibit the binding of the protein to its normal cellular target. Thus, in both paper the authors had knowledge of what the normal cellular target looks like. An inhibitory antibody would indicate that the antibody binds at the same location as the cellular target. Since the cellular target of huntingtin protein is not known the antibodies of the instant invention cannot be tested to see if they would inhibit the interaction between the huntingtin protein and a cellular target.

Appellant argues that their evidence need not be conclusive but merely convincing to one skilled in the art. Citing *In re Brandstadter* 179 USPQ 286 (CCPA 1973). In response, the references and declaration provided by applicants have been considered but they did not

overcome the finding by the examiner that the methods set out in the claims are not enabled. In this instance the only knowledge of the antibodies set out in the specification is that the antibodies bind to the polyglutamine expansion of the huntingtin protein. Because the cellular target of huntingtin protein is not known the ordinary artisan cannot be convinced that the antibody can act as a surrogate cellular target because the antibody cannot be compared to the binding of the huntingtin protein to its cellular target.

The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). In this case, the declaration is only speculative and does not provide evidence of a correlation between the polyglutamine expansion and the binding site of the cellular target. The 1.132 Declaration by Ross Stein does not overcome the rejection because the declaration does not actually indicate that the antibody binds to the polyglutamine expansion protein at the same location where the cellular target binds to the polyglutamine expansion protein. Additionally, binding between polyglutamine repeat regions does not provide information regarding the binding of huntingtin to the cellular target. "It is not unreasonable to assume that the binding site on the antibody might have structural features and binding properties for polyglutamine that are similar to the binding sites on the cellular proteins that mediate the toxic effect of the polyglutamine" (see Ross Stein declaration paragraph 4). At best the declaration merely speculates that the antibody may bind in the same location as the cellular receptor. The declaration does not provide a correlation that would indicate that a compound that interferes with the antibody binding to the polyglutamine

expansion of huntingtin would interfere with the binding of the polyglutamine expansion protein to the normal cellular target.

Appellants argue that the finding of lack of enablement is a personal opinion of the Examiner unsupported by any evidence or scientific reasoning. In response, the rejection is based on the basic idea that in order for an antibody to function as a "surrogate cellular target' or "surrogate cellular receptor," the antibody will need to bind to the area in the protein that is actually responsible for the interaction between the protein-receptor or protein-cellular target. This basic idea, which Appellant claims is not supported by any evidence or scientific reasoning (see Appeal Brief, page 8, lines 21 and 22), is indeed supported by evidence and sound scientific reasoning for the reasons set out by the Examiner and corroborated for the same reasons (or logic) in the South et al. reference (see page 144, column 2, lines 33 to page 145, column 1, line 16). In the South et al. reference the authors used an antibody as a "surrogate receptor," the antibody was chosen for its ability to block the protein-receptor (vWF-GPIb) interaction. "This antibody was selected based on is ability to block the vWF-GPIb interaction by binding to a peptide sequence spanning 474-488 of the mature vWF subunit" (see 145, column 1, lines 3-5). It was previously known that regions 474-488 and 694-708 of the vWF protein are involved in the binding of vWF to GPIb (see 144, column 2, lines 38-40). Thus, to be a "surrogate cellular target" it is necessary to show that the antibody inhibits the binding between the cellular target and the huntingtin protein. Only by showing that the antibody actually inhibits the normal interaction between the protein and its cellular target can the antibody serve as a "surrogate target"

(2) Response to argument that "no conclusions as to the enablement of the instant claims can be drawn from the Heiser et al. reference."

The Heiser et al. reference was cited because it provides background information of what was known about Huntington disease and the huntingtin protein at the time the invention was made. The reference indicates that the "causal relationship between aggregate and formation and disease has not been proven, genetic, neuropahtological, and biochemical evidence indicate that formation of insoluble protein aggregates plays an important role in the cellular distortions underlying HD and related glutamine-repeat disordered" (see page 6739, column 1, 2nd paragraph). Thus, the cause of Huntington disease is not known and neither is the structure of the cellular target of the huntingtin protein.

Appellants further argue that the antibody disclosed by Heiser et al., the 1C2 antibody, differs from the antibodies of the instant invention. The Office has never disputed that the antibodies of the instant invention differ from the antibodies found in the prior art. The parent application of the instant invention issued claims drawn to antibodies binding to the polyglutamine expansion protein. In this instance, the Heiser et al. reference provides evidence that the prior art did not know the structure of the cellular target for huntingtin protein. The prior art also does not know what the cause of the disease is, the only thing the prior art has established that in people with the Huntington disease they have observed an agglutination of the huntingtin protein. Thus, the reference is relevant to show that the prior art does not known what causes the disease and that the cellular target of huntingtin protein is also not known. In order for the instant invention to be enabled requires knowledge of the cellular target of huntingtin protein, so that the antibody can be shown to be a surrogate for that cellular target.

(3) Response to argument that "antibodies specific for a protein can serve as a surrogate for binding of that protein to a second protein."

Appellants' argument is that the antibodies serve as a "surrogate" receptor or cellular target in the instant method claims. A "surrogate" is defined in Webster's online dictionary as "a person appointed to act in place of another: delegate, deputy, substitute; something that replaces or serves as a substitute for another; an artificial or synthetic product used as a substitute for a natural product." Thus, if the antibody is to serve as a surrogate (substitute) for the cellular receptor or a substitute for the cellular target the ordinary artisan would need to know what the cellular target or receptor is, in order to determine that the antibody can fulfill the role of a surrogate (substitute).

Appellant has provided two references as evidencing that an antibody can serve as a "surrogate" for another protein. The Office does not dispute that an antibody, can act as a substitute for a cellular target. However, what is required in order to use an antibody as a substitute or surrogate is knowledge of the normal protein interaction that the protein has with the cellular receptor or cellular target in some circumstances. In this instance, neither the specification nor the art has provided any information regarding the epitopes of the huntingtin protein that are actually involved in the binding of the cellular target to the huntingtin protein. In both references cited by Appellant, Kaji et al. and South et al., it was shown that the antibody binds in the position on the protein that is also involved in the binding of the protein to the cellular target. This critical information about the antibody interaction with huntingtin protein is lacking in the instant specification.

Kaji et al. has determined that the antibody that inhibits the chemotactic activity of monocyte chemoattractant protein (MCP-1) can be used to screen for peptide motifs that are inhibitors of the chemotactic activity. "[I]nhibitory monoclonal antibodies may display moieties that mimic a receptor/ligand-like three dimensional structure. This pseudoreceptor/ligand should be able to bind to natural ligand/receptor molecules" (see Kaji et al. page 577, column 1, line 2-6). The critical difference between the cited Kaji et al. paper and the instant specification is that in the cited paper the authors have associated an activity that is inhibited with the antibody used in their screening assay. In the Kaji et al. paper "the anti-MCP-1 monoclonal antibodies inhibit the chemotactic activity of the MCP-1 protein" (see page 577, column 2, lines 5-8). Because the antibody inhibits the activity of the protein the authors know that the antibody binds to a part of the protein that is involved in the receptor-ligand interaction and not to some portion of the protein that is not involved in the binding activity.

South et al. has determined that the antibody that recognizes the GPIb domain of the vWF can be used to screen for peptide inhibitors that inhibit the binding between vEF-GPIb binding. The critical difference between the cited paper and the instant specification is that in the South et al. reference the authors actually knew that the antibody binds to the vWF protein at a region that is required for the binding of the vWF protein to the GPIb receptor (see page 144, column 2, lines 33 to page 145, column 1, line 16). In the reference, a murine monoclonal antibody was used in the screening of peptide libraries for potential inhibitors. This murine monoclonal antibody was selected because of its ability to block the vWF (protein) – GPIb (receptor) interaction. In the reference, the antibody was able to prevent the binding of the protein to its

cellular target indicating that the antibody binds at the same location that is required for the protein-receptor interaction.

Both the South et al. and the Kaji et al. papers explained that antibodies that served as the surrogate receptor are also antibodies that inhibit the protein from binding the cellular target. The examiner has rejected the instant invention as not being enabled because the instant specification has not shown that the antibodies of the present invention actually inhibit the binding of the huntingtin protein to its cellular target. The ordinary artisan cannot determine if the antibodies of the instant invention would inhibit the binding of the huntingtin protein to the cellular target because the cellular target for huntingtin protein is not known.

According to Appellants arguments the examiner has misunderstood the claimed invention. "The antibodies in the claimed method do not serve to prevent the binding of the polyglutamine containing protein to its cellular target" (see Appeal Brief page 11, lines 3-4). Both the South et al. and the Kaji et al. papers explained that antibodies that function as the surrogate receptor are also able to prevent the binding of the protein to the receptor. Thus, by Appellants own admission the antibodies of the instant invention cannot serve as a "surrogate cellular target" because the antibodies do not prevent the binding of the polyglutamine repeat containing protein (huntingtin) to the cellular target.

Because the instant specification has not provided any evidence that the antibody binds atthe same place on the huntingtin protein that is responsible for the binding of the huntingtin protein to the cellular target, the instant invention is not enabled as a method of screening for inhibitors between the huntingtin protein and the unknown and undisclosed cellular target.

(4) Response to argument that "those skilled in the art would find it reasonable to use the assay methods to identify agents that inhibit binding of a protein containing a polyglutamine expansion to its cellular receptor."

Both the South et al. and the Kaji et al reference teach that only those antibodies that inhibit the activity of the protein are able to function as "surrogate" receptor in screening assays. Because the cellular receptor for huntingtin protein is not known the ordinary artisan cannot test if the disclosed antibodies actually inhibit the binding of the huntingtin protein to its cellular target. Therefore it cannot be known whether these antibodies can serve as a "surrogate." The antibodies disclosed in the instant specification may bind huntingtin protein, or the polyglutamine expansion of the huntingtin protein at a location that is not involved the binding of the protein to the cellular target. Because the specification lacks the correlation that the antibodies bind at the same location that binds the cellular target the antibodies have not been demonstrated to be surrogates.

The 1.132 Declaration by Ross Stein does not overcome the rejection because the declaration does not actually indicate that the antibody binding to the polyglutamine expansion protein bind in the same location where the cellular target binds to the polyglutamine expansion protein. "The antibody that will be used is the in this assay has specific binding for the toxic conformation of the polyglutamine." The toxic conformation of the polyglutamine is the fibril formation. "It is not unreasonable to assume that the binding site on the antibody might have structural features and binding properties for polyglutamine that are similar to the binding sites on the cellular proteins that mediate the toxic effect of the polyglutamine." The declaration only speculates that the antibody could bind at the same target site but this does not necessarily have

to be the case. The declaration does not provide any correlation that would indicate that a compound that interferes with the antibody binding to the polyglutamine expansion of huntingtin would interfere with the binding of the polyglutamine expansion protein to the normal cellular target.

(11) Related Proceeding(s) Appendix

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 5/26/06

Conferees:

Bruce Campell, SPE

Christina Chan, SPE

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600